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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/121,587	07/23/1998	THOMAS J. CHAMBERS	06132/033003	3485

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EXAMINER
ZEMAN, ROBERT A

ART UNIT	PAPER NUMBER
1645	41

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Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Advisory Action	Application No.	Applicant(s)	
	09/121,587	CHAMBERS ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 14 May 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *see attached*.

3. ☐ Applicant's reply has overcome the following rejection(s):

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: none

   Claim(s) objected to: none

   Claim(s) rejected: *1,2,6-10 and 14-16*.

   Claim(s) withdrawn from consideration: *3-5,11-13 and 17-29*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

ADVISORY ACTION

The amendment after final rejection filed on 5-14-2003 has not been entered.

The proposed amendment raises new issues that would require further consideration and/or search. Specifically, the limitation "that the capsid protein of said chimeric virus is from yellow fever virus" requires a new search.

Since Applicant's arguments are based on the proposed amendment and points addressed (and deemed unpersuasive) in the previous Office action all rejections are maintained for reasons of record. A summary of said rejections follows.

Claim Rejections Maintained

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

The provisional rejection of claims 1, 2, 6-10 and 14-16 under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 2, 6-7, 9-11 and 15-18 of copending Application No. 09/452638 is maintained for reasons of record. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Applicant argues:

1. The rejection should be withdrawn in accordance with M.P.E.P. 822.01.

Applicant's arguments have been fully considered and deemed non-persuasive. Since the aforementioned rejection is not the sole remaining rejection M.P.E.P. 822.01 does not apply.

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 9-10 and 14-16 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for therapeutic/prophylactic use of the chimeric virus YF/JE SA_{14}-14-2 RMS **or YF/$JE_{Nakayama}$** against Japanese encephalitis virus infection, does not reasonably provide enablement for the therapeutic/prophylactic use of **any other** chimeric flavivirus, nor does it provide enablement for the therapeutic/prophylactic use of the chimeric virus YF/JE SA_{14}-14-2 RMS or **YF/$JE_{Nakayama}$** against anything other than Japanese encephalitis virus infection is maintained for reasons of record.

Applicant argues:

1. The specification discloses the efficacy of the YF/JE Nakayama chimera.

2. The paper by Guirakhoo et al. (Virology 74(12):5477-5485, **2000**) discloses the efficacy of an YF/Dengue 2 chimera.

3. The paper by Arroyo et al. (Trends Mol. Med. 7:2350-2354, **2001**) discloses the efficacy of an YF/West Nile 2 chimera.

Applicant's arguments have been fully considered and deemed non-persuasive.

Applicant's assertion that the specification demonstrated the efficacy of the YF/JE Nakayama chimera is well founded. Consequently, the aforementioned rejection has been modified. However, contrary to Applicant's assertion, the post filing references by Guirakhoo et al. and Arroyo et al. do not demonstrate that the specification would enable any person skilled in the art to which it pertains, or with which it is most nearly connected (at the time of the invention), to use the invention commensurate in scope with these claims Said reference do disclose two chimeras that have efficacy as a prophylactic. However, based on the instant specification, one of skill in the art would not have been able to predict that said chimeras (or any other chimera) would be effective prophylactics. As noted previously, the instant specification fails to provide direction (i.e. which sequences must be added to the YF backbone etc.) on which chimeric viruses, other than. SA_{14}-14-2 RMS **or** $YF/JE_{Nakayama}$ would elicit a therapeutic or prophylactic response. Moreover, it appears that the primers utilized by Guirakhoo et al. differ from the ones disclosed in the instant application for the generation of an YF/DEN-2 chimera (see page 63 of the specification and page 5478 of Guirakhoo et al.). Consequently, given the lack of success in the art, the lack of working examples and the unpredictability of the generation of a therapeutic or prophylactic response in a living organism, the specification is not enabling for the therapeutic/prophylactic use of chimeric flavivirus other than SA_{14}-14-2 RMS **or** $YF/JE_{Nakayama}$, nor does it provide enablement for the therapeutic/prophylactic use of the chimeric virus YF/JE SA_{14}-14-2 RMS or $YF/JE_{Nakayama}$ against anything other than Japanese encephalitis virus infection.

It should be noted that the proposed amendment, if entered, would have been sufficient to overcome this rejection.

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The instant claims are drawn to a chimeric, live, infectious virus comprising a yellow fever virus (first virus) in which the nucleotide sequence encoding the prM-E protein is modified such that the functional YF virus prM-E protein is not expressed, and integrated into said YF virus a nucleotide sequence encoding a prM-E protein of a second, different flavivirus,

specifically the Japanese Encephalitis virus, so that the prM-E of said second virus is expressed. The claims are further drawn to the chimeric virus wherein the nucleotide sequence encoding the prM-E protein of the second flavivirus comprises a mutation that prevents prM cleavage to produce M protein while maintaining the NS2-B-3 protease recognition site and signal sequences and cleavage sites at the C/prM and E/NS1 junctions.

The rejection of claims 1-2, 6-10 and 14-16 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Lai et al. (WO 93/06214—IDS-22) is maintained for reasons of record.

Applicant argues:

1. The focus of Lai et al. is chimeras that include structural proteins from tick-borne encephalitis virus and non-structural proteins of dengue virus, as well as intertypic dengue chimeras.

2. In most of the chimeras described in the Lai publication, all 3 structural proteins (C, prM and E) of one flavivirus is replaced with those of another.

3. Lai et al. disclose only two specific examples of chimeras including non-structural and capsid proteins from the first virus and pre-membrane and envelope proteins from another virus. Said examples utilize a dengue virus as the first virus and either TBEV or Japanese encephalitis virus as the second virus.

4. Lai et al. disclose on page 21 lines, 24-33 that said chimeras are unexpected and does not suggest that such chimeras be made using other flaviviruses such as yellow fever virus as the source of the non-structural and capsid proteins.

5. The only context in which yellow fever virus is mentioned by Lai et al. is in a chimera in which the sources of all structural and all non-structural proteins are different.

6. Lai et al. do not describe a yellow fever based chimera that includes the non-structural and capsid proteins of the yellow fever virus and the pre-membrane and envelope proteins of another flavivirus as is required by the instant claims.

7. The dengue-based chimera described by Lai et al. have the TBEV signal sequence that lies between the prM and C in addition to the TBEV prM and E proteins.

8. This approach when used with a Yellow virus backbone (first virus) and dengue as the source of the structural sequence does not produce a viable chimera. Hence, the prior art teaches away from the approach of the instant invention.

Applicant's arguments have been fully considered and deemed non-persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the capsid protein must be from the first virus (i.e. yellow fever virus) are not recited in the rejected claim(s) since the proposed amendment has not been entered. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

As outlined previously, Lai et al. disclose an attenuated chimeric flavivirus particle comprising a region of nucleotide sequences encoding the non-structural proteins (NS) of the yellow fever virus and a region of nucleotide sequences encoding the structural protein prM-E of a flavivirus selected from a dengue virus (serotype 1, 2, 3 and 4), Japanese encephalitis virus,

tick-borne encephalitis virus (specifically) and a flavivirus (generally). Lai et al. specifically disclose the DNA fragment that encodes a dengue virus protein comprising mutations at the C-terminal of the NS1 gene, resulting in the prevention of the NS1 protein cleavage (see examples 8-12). Lai et al. further disclose the use of said chimeric flaviviruses as a vaccine (see example 21) and methods of producing said chimeric viruses recombinantly (see example 17). While Lai et al. do not explicitly disclose methodologies (i.e. provide working examples) using the Yellow Fever virus and the Japanese encephalitis virus such a chimeric was contemplated (see claim 38). Moreover, Lai et al. disclose 'a chimeric virus for use in vaccine preparation having a genome comprising nucleic acid sequences encoding at least one structural protein from one flavivirus and nucleic acid sequences encoding nonstructural proteins from another (see abstract and page 6, li9nes 18-25). Therefore, while not explicitly disclosed in the working examples, the Yellow Fever/Japanese encephalitis combination would be an obvious variant of the chimerics disclosed by Lai et al.

The rejection of claims 1-2, 6-10 and 14-16 under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Lai et al. (U. S. Patent 6,184,024—IDS-29) is maintained for reasons of record.

Applicant argues:

1. In most of the chimeras described in the Lai publication, all 3 structural proteins (C, prM and E) of one flavivirus is replaced with those of another.

2. Lai et al. disclose only two specific examples of chimeras including non-structural and capsid proteins from the first virus and pre-membrane and envelope proteins from another virus. Said examples utilize a dengue virus as the first virus and either TBEV or Japanese encephalitis virus as the second virus.

3. The only context in which yellow fever virus is mentioned by Lai et al. is in a chimera in which the sources of all structural and all non-structural proteins are different.

4. Lai et al. does not describe a yellow fever based chimera that includes the non structural and capsid proteins of the yellow fever virus and the pre-membrane and envelope proteins of another flavivirus as is required by the instant claims.

Applicant's arguments have been fully considered and deemed non-persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the capsid protein must be from the first virus (i.e. yellow fever virus) are not recited in the rejected claim(s) since the proposed amendment has not been entered. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

As outlined previously, Lai et al. disclose an attenuated chimeric flavivirus particle comprising a region of nucleotide sequences encoding the non-structural proteins (NS) of the yellow fever virus and a region of nucleotide sequences encoding the structural protein prM-E of a flavivirus selected from a dengue virus (serotype 1, 2, 3 and 4), Japanese encephalitis virus, tick-borne encephalitis virus (specifically) and a flavivirus (generally). Lai et al. specifically

disclose the DNA fragment that encodes a dengue virus protein comprising mutations at the C-terminal of the NS1 gene, resulting in the prevention of the NS1 protein cleavage or 3' mutations resulting in reduced glycosylation of prM, E or NS1 resulting in reduced cleavage of the prM protein (see examples 9-16). Lai et al. further disclose the use of said chimeric flaviviruses as a vaccine (see example 23-24) and methods of producing said chimeric viruses recombinantly (see example 22). While Lai et al. do not explicitly disclose methodologies (i.e. provide working examples) using the Yellow Fever virus and the Japanese encephalitis virus such a chimeric was contemplated (see claims 1 and 8). Moreover, Lai et al. disclose 'a chimeric virus for use in vaccine preparation having a genome comprising nucleic acid sequences encoding at least one structural protein from one flavivirus and nucleic acid sequences encoding nonstructural proteins from another (see abstract and column 5, lines 58-67). Therefore, while not explicitly disclosed in the working examples, the Yellow Fever/Japanese encephalitis combination would be an obvious variant of the chimerics disclosed by Lai et al.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Robert A. Zeman
June 9, 2003

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